HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Statins and Hepatocellular Carcinoma Protection

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G&H What have studies found regarding the possible relationship between statins and hepatocellular carcinoma protection?

DK Approximately 10 years ago, the first large study looking at the potential association between statins and hepatocellular carcinoma (HCC) was conducted by Dr Hashem B. El-Serag and colleagues in a cohort of patients with diabetes. The researchers found that in individuals with diabetes, who potentially have a higher risk of HCC than individuals without diabetes, exposure to a statin was associated with a significant reduction in the subsequent risk of HCC. According to the most conservative estimate by this group of researchers, receipt of any statin was associated with an approximately 26% reduction in HCC risk. After adjusting for covariates associated with advanced liver disease, the researchers found that statins had a slightly stronger effect.

This protective effect has been fairly consistently replicated over time in studies with slightly different methodologies by other groups in the United States, as well as in studies from other areas, such as Korea, Taiwan, Hong Kong, and Sweden, and in different patient populations. Several different groups have looked at statin exposure in various US populations, both involving Veterans Affairs (VA) patients and non-VA patients. The largest non-VA study was conducted by Dr Katherine A. McGlynn and colleagues in a population of health maintenance organization members. The researchers found that using statins seemed to be highly associated with not developing HCC. Around the same time, a Swedish study that examined approximately 4000 HCC cases and approximately 20,000 control patients found that statin exposure was associated with reduced HCC risk but, in a similar control population, had no association with reduced colon cancer risk. These data suggest that the protective effect of statins may be specific to HCC. Similarly, a landmark analysis from Hong Kong looked at approximately 75,000 patients with hepatitis B virus infection and found an approximately 32% reduction in HCC risk associated with statin exposure.

G&H Are there any limitations to these studies that should be taken into account?

DK The issue with large population-based studies is that one of the key indications for statin utilization is hyperlipidemia. Cholesterol is produced by the liver, so individuals with more advanced liver disease who are most at risk for HCC are less likely to manifest hyperlipidemia and are, therefore, also less likely to receive statins. It is challenging to interpret retrospective studies due to this confounding by indication.

Other shortcomings of these studies involve the limitations of the available laboratory and other clinical data for optimally matching cases and controls, as well as the use of relatively brief requirements for defining the duration of time for statin exposure (ie, 30-90 days, which is too short of a time to plausibly exert a biologic effect).

G&H Why might statins have a protective effect on HCC?

DK Multiple groups have looked at various HCC cell lines and found that statins modulate specific molecular

pathways in these lines that reduce the ability of HCC cells to proliferate in vivo. Some of the effects are cell line–specific, but, in general, statins affect pathways proximal to mitogen-activated protein kinase pathways, and the effect on cell line growth seems to be related to these pathways. There is also some early work from other groups looking at cholesterol transport defects that are associated with reduced HCC growth. HCC cell lines seem to be very dependent on the ability to synthesize cholesterol, as cells need to make more plasma membranes and organelles to divide, and cholesterol is a critical part of cell membranes. Because dividing cells need cholesterol, it is not surprising that inhibiting cholesterol synthesis would have a potential anticancer effect. However, it is not clear that what has been observed in vitro specifically translates to what has been observed in retrospective studies.

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G&H According to the research currently available, might some types of statins have a greater protective benefit for HCC than other types of statins?

DK There has been some interest regarding whether lipophilic or hydrophilic statins have more of a protective effect. Some provocative data were presented by Dr Tracey Simon and colleagues at last year's meeting of the American Association for the Study of Liver Diseases. Using a Swedish health care registry, the researchers found that lipophilic statins, but not hydrophilic statins, seemed to confer a protective effect on a population level for preventing HCC. However, I think that caution is needed in interpreting these data because of the significant confounding by indication discussed earlier. Patients with more significant liver disease would not necessarily be exposed to statins. Therefore, the association with protection may not reflect the effect of the drug but rather differences in risk between the exposed and unexposed populations.

To try to adjust for this confounding by indication, my colleagues and I performed a preliminary evaluation of the association of statins and death, decompensation, and HCC using risk-set matching and inverse probability weighting in a population with cirrhosis identified from VA data, and the results were recently published online ahead of print publication in *Gastroenterology*. Instead of basing statin exposure on a certain number of prescriptions filled, we evaluated statin use as continuous exposure because we thought that the effect of statins would increase cumulatively over the course of the time period rather than be mediated by a short period of exposure of 30 to 90 days, which most studies have done. This conservative analysis found a statistically significant association of statins on overall survival in a cohort of approximately 70,000 patients with cirrhosis. When looking at overall survival, there was no difference between lipophilic or hydrophilic statin exposure, suggesting that once an individual has cirrhosis, the type of statin is likely irrelevant.

Similar findings, that the type of statin does not seem to affect the benefit in high-risk individuals, were identified by a Korean case-control study. Thus, there is currently no evidence that a particular statin or group of statins is more protective than another in patients with existing liver disease.

G&H What other findings were reported from your study?

DK After significant adjustment for liver-related covariates, having at least 90 days of additional exposure of a statin was strongly associated with reduced HCC rates in existing users of statins (patients on a statin before being diagnosed with cirrhosis) with Child-Pugh A and B disease. In new initiators of statins (statins started after cirrhosis was diagnosed), we did not find a significant association, although there was a trend toward reduced HCC development in Child-Pugh A, but not Child-Pugh B, patients. In the combined cohort, we measured an approximately 10% reduction in HCC risk for every year of exposure to statins. In Child-Pugh C patients, statins were not associated with a reduction in HCC or decompensation. Thus, once patients have cirrhosis, it is probably too late for statins to work. Only patients who have Child-Pugh A and Child-Pugh B likely benefit. We also found some evidence that statin use in Child-Pugh C patients was probably harmful.

G&H Based on all of the data currently available, what is the increment of the protective benefit that statins seem to provide for HCC?

DK It is difficult to make a specific, overall estimate of the increment of benefit because of the different methodologies used in the retrospective studies that have been conducted. However, based on the data that my colleagues and I have reported, I estimate that there is an approximately 8% to 10% HCC risk reduction per year for every year of cumulative statin exposure. This is a more conservative estimate than what other studies suggest, but would be biologically plausible and would reflect what we typically observe clinically.

G&H Should statins be started in stage III or IV disease?

DK It is unlikely that statins would have a significant biologic effect on patients with very advanced cancer, such as stage III or IV disease. There is also emerging evidence that in patients with any compromised liver function, such as Child-Pugh C, statins increase the risk of death. In contrast, data on patients with earlier stages of cancer suggest that statins might have a palliative effect on HCC. However, some of these studies were retrospective and biased, as statins were not given to patients who were very ill; thus, it might appear that patients did not live as long without statins, but the difference in survival was related to the baseline sickness of the unexposed patients. Therefore, these studies should be viewed with skepticism until prospective research is available.

In addition, there are some retrospective data suggesting that patients who continued statins after they were diagnosed with HCC seemed to have a decreased risk of cancer-specific mortality, with a hazard ratio of approximately 0.85 and irrespective of the intensity of the statin. However, the quality of these data is modest.

G&H What is the optimal dose and length of statin therapy?

DK The optimal dose and length of statin therapy is unknown and needs to be tested in a prospective manner. The only prospective data currently available are from a study conducted by Dr Juan G. Abraldes and colleagues in patients with variceal hemorrhage who were prescribed simvastatin in addition to standard of care for variceal bleeding. The researchers initiated patients on a 20-mg daily simvastatin lead-in phase and then increased the dose to 40 mg if the patients were tolerating therapy. Over 2 years, there was a significant reduction in overall death, but not a reduction in variceal rebleeding, which was the primary endpoint of the study. Because the study was not designed to test for improvement in overall survival, there are concerns that the results might be a statistical fluke. Therefore, these prospective data need to be reproduced before any recommendation can be made. Nevertheless, these results provide a potential dose regimen for patients with cirrhosis that can be used in future prospective trials.

G&H Should patients at risk for HCC be prescribed a statin solely for the prevention of the disease?

DK We do not have adequate high-quality data to make any recommendation at this time that a patient with cirrhosis should be prophylaxed with a statin to prevent HCC. Until there are prospective, randomized, controlled data showing that this approach is both safe and effective, I would caution against overinterpreting the retrospective data that exist.

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G&H What adverse events are associated with statin use?

DK Myopathy is the biggest concern and can sometimes be severe. According to data from the LIVERHOPE Consortium in Europe, approximately 20% of patients with Child-Pugh C cirrhosis who were given statins developed fairly significant myopathy requiring dose reduction or elimination. There is also a risk of pancreatitis, although it is fairly rare.

There has also been excessive concern regarding possible hepatotoxicity from statins. However, this concern was largely based on the misinterpretation of abnormal liver enzymes in large statin trials. Most of the abnormalities were because the study subjects had fatty liver and, thus, had abnormal liver test results because of their liver disease, not because of their statin use. In many cases, statin use in these patients led to the improvement of liver enzymes. In fact, hepatotoxicity from statins is exceedingly rare; most data suggest that the risk is close to 1 in 100,000 patients. Well-compensated cirrhotic patients are unlikely to develop hepatotoxicity from statins.

G&H What are the next steps in research?

DK Long-term, prospective, multicenter, randomized, controlled studies are needed to evaluate the impact of statins in patients with cirrhosis using endpoints that include HCC. Currently, the LIVERHOPE Consortium is conducting one such study in patients with decompensated liver disease to see whether there is an improvement in outcome once patients have decompensated. There has been some concern regarding safety signals in this population, but the study is ongoing. There are also 2 ongoing randomized, controlled trials from Cedars-Sinai Medical Center prospectively studying the impact of statins on HCC in patients with cirrhosis. No data are yet available. However, these are single-center, relatively small studies that are likely to be underpowered to find a benefit of statins. There are incipient efforts by VA investigators to conduct a multicenter trial, but none to date have been funded.

Dr Kaplan has no relevant conflicts of interest to disclose.

Suggested Reading

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